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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,263	09/28/2005	Toshihiro Nakashima	NAKASHIMA=6	3356

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EXAMINER	
OGUNBIYI, OLUWATOSIN A	

ART UNIT	PAPER NUMBER
1645	

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10/07/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,263	NAKASHIMA ET AL.	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *6-8,16,17,21 and 23* is/are pending in the application.

5a) Of the above claim(s) *23* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *6-8,16,17 and 21* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/GB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A*.

Notice of Allowance Vacated

1. Applicant is advised that the Notice of Allowance mailed 5/27/11 is vacated. If the issue fee has already been paid, applicant may request a refund or request that the fee be credited to a deposit account. However, applicant may wait until the application is either found allowable or held abandoned. If allowed, upon receipt of a new Notice of Allowance, applicant may request that the previously submitted issue fee be applied. If abandoned, applicant may request refund or credit to a specified Deposit Account.

Claims 6-8, 16-17, 21 and 23 are pending. Claim 23 is withdrawn from consideration as being directed to a non-elected invention. See 37CFR 1.142(b) and MPEP 821.03.

Claim Rejections Withdrawn

2. The rejection of claim 21 under 35 U.S.C. 112, first paragraph (scope of enablement) is withdrawn in view of the amendment to the claim.

3. The rejection of claim 8 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 4 of copending Application No. 12/644952 ('952) is withdrawn in view of the cancellation of claim 4 in the '952 application.

New Claim Rejections

Claim Rejections - 35 USC § 102 and 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claim 8 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sasaki et al. EP 1055429 A1 published 11/29/2000 cited in IDS (international publication number WO 99/40935) in view of Terman et al US6180097 1/30/01.

Sasaki et al teaches a modified Staphylococcal enterotoxin B (SEB). Sasaki teaches said modified enterotoxin with arbitrary amino acid substitutions at an epitope recognition site (p.3 paragraph 12 -14, p. 4 paragraphs 17, 18, 19, 23, p. 8 table 3). Sasaki teaches said modified SEB wherein Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr (p.3 paragraph 12, p. 8 table 3). Since Sasaki discloses a modified SEB as instantly claimed, for example, Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr, said modified SEB of Sasaki et al inherently possess reduced reactivity with a neutralizing anti-SEB

antibody. The sequence of the SEB used to make the modified SEB inherently has the amino acid sequence as set forth in instant SEQ ID NO: 1. This is evidenced by the fact that the instant specification discloses that the modified SEB N23Y (a mutant with substitution of the asparagine residue at 23 position of SEB with tyrosine residue) used in the examples is known and disclosed in WO99/40935 which is the international publication number for Sasaki et al. EP 1055429 A1 published 11/29/2000.

In the alternative, it would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to have obtained the wild type sequence of SEB as set forth in SEQ ID NO: 1 and modify at position 23 as disclosed by Sasaki et al in order arrive at a modified SEB that has reduced immunological responsiveness to SEB without inducing elimination of T cells having specific Vβ component. Said modified SEB can be used to treat rheumatoid arthritis. See Sasaki et al in abstract and claims.

The closest prior art that discloses the amino acid sequence of SEB is by Terman et al and the difference between the prior art wild type sequence (see Appendix A) and that of instant SEQ ID NO: 1 is a single amino acid mismatch at position 123). SEQ ID NO: 1 would have been prima facie obvious to obtain and is prima facie obvious over the SEB amino acid sequence disclosed by Terman et al. There would have been only a limited number of species of the SEB protein and the generic teaching to modify a SEB protein for various advantageous reasons would make the species of SEB protein i.e. SEQ ID NO: 1 prima facie obvious.

5. Claims 6-7 are rejected under 35 U.S.C. 103(a) as being obvious over Nishi et al. The Journal of Immunology, 1997, 1558:247-254 cited in IDS in view of Terman et al US6180097 1/30/01.

Nishi et al teaches a modified Staphylococcal enterotoxin B (SEB). Nishi teaches a modified SEB wherein the amino acid substitution was introduced within a region from Lys at 226-position to Lys at 229-position in the amino acid sequence of SEB (p.250 column 1 last bridging paragraph to column 2). Nishi teaches that said modified enterotoxin has reduced

reactivity with an IgG antibody (p. 252 fig. 6 and column 2 last two paragraphs to p. 253 first paragraph).

Nishi does not teach said modified SEB with the amino acid sequence from 226-229 of SEB (SEQ ID NO: 1) is Ala Thr Thr Gln or Lys Arg Ile Ile.

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to have obtained the wild type sequence of SEB as set forth in SEQ ID NO: 1 and to introduce other amino acid substitutions in position 226-229 of said SEB thus resulting in the instant invention with a reasonable expectation of success. The motivation to do so is that Nishi teaches that amino acid residues 226-229 of SEB are recognized by antibody to SEB and that amino acid substitutions in position 226-229 results in a SEB with reduced activity to a SEB antibody. Thus, giving the teachings of Nishi, one of ordinary skill in the art can screen different combinations of amino acid substitutions in position 226-229 (epitope recognition site) using methods known in the art for introducing random or arbitrary substitutions into SEB to arrive at a modified SEB with reduced reactivity with SEB neutralizing antibody with a reasonable expectation of success.

The closest prior art that discloses the amino acid sequence of unmodified SEB is by Terman et al and the difference between the prior art wild type sequence (see Appendix A) and that of instant SEQ ID NO: 1 is a single amino acid mismatch at position 123). SEQ ID NO: 1 would have been prima facie obvious to obtain and is prima facie obvious over the SEB amino acid sequence disclosed by Terman et al. There would have been only a limited number of species of the SEB protein and the generic teaching to modify a SEB protein for various advantageous reasons would make the species of SEB protein i.e. SEQ ID NO: 1 prima facie obvious.

6. Claims 16-17 are rejected under 35 U.S.C. 103(a) as being obvious over Nishi et al. The Journal of Immunology, 1997, 1558:247-254 cited in IDS and Terman et al US6180097 1/30/01 as applied to claims 6-7, above, further in view of Sasaki et al EP 1055429 A1 published 11/29/2000, cited in IDS.

The combination of Nishi and Terman et al is set forth supra.

Said combination does not teach that Asn residue position 23 is substituted with Tyr

Sasaki teaches a modified SEB wherein Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr (p.3 paragraph 12, p. 8 table 3). Sasaki teaches that said modified SEB is used for a remedy for immunopathy such as rheumatoid arthritis because said amino acid substitution at position 23 results in a SEB that has inhibitory activity on T cell activation with reduced toxicity (see abstract and p. 3 paragraph 9, 10, 21). Sasaki also teaches how to introduce amino acid substitutions into SEB.

It would also have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to additionally introduce an amino acid substitution at residue 23 i.e. replacing Asn with Tyr in the modified SEB of the combination of Nishi et al and Terman et al. The motivation to do so is that Sasaki et al teach that such an amino acid substitution results in a SEB superantigen that is less toxic without introduction of the pathological effects of said superantigen.

7. Claim 21 is rejected under 35 U.S.C. 103(a) as being obvious over Nishi et al. The Journal of Immunology, 1997, 1558:247-254 cited in IDS in view Terman et al US 6180097 1/30/01 and Sasaki et al EP 1055429 A1 published 11/29/2000 cited in IDS.

Nishi et al teaches a modified Staphylococcal enterotoxin B (SEB). Nishi teaches said modified enterotoxin with arbitrary amino acid substitutions at an epitope recognition site (p.250 column 1 last bridging paragraph to column 2). Nishi teaches a modified SEB wherein the amino acid substitution was introduced within a region from Lys at 226-position to Lys at 229-position in the amino acid sequence of SEB (p.250 column 1 last bridging paragraph to column 2). Nishi teaches that said modified enterotoxin has reduced reactivity with an IgG antibody (p. 252 fig. 6 and column 2 last two paragraphs to p. 253 first paragraph).

Nishi does not teach said modified SEB with the amino acid sequence from 226-229 of SEB (SEQ ID NO: 1) is Ala Thr Thr Gln or Lys Arg Ile Ile and does not teach further modifications wherein Asn at 23 position in the amino acid sequence of said modified SEB (SEQ ID NO: 1) is substituted with Tyr.

Sasaki teaches a modified SEB wherein Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr (p.3 paragraph 12, p. 8 table 3). Sasaki teaches that said modified SEB is used for a remedy for immunopathy such as rheumatoid arthritis because said amino acid substitution at position 23 results in a SEB that has inhibitory activity on T cell activation with reduced toxicity (see abstract and p. 3 paragraph 9, 10, 21). Sasaki also teaches how to introduce amino acid substitutions into SEB.

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to have obtained the wild type sequence of SEB as set forth in SEQ ID NO: 1, sequence it and modify the wild type staphylococcal enterotoxin B sequence to introduce other amino acid substitutions in position 226-229 and introduce tyr at position 23 in lieu of Asn, thus resulting in the instant invention with a reasonable expectation of success. The motivation to do so is that giving the teachings of Nishi, one of ordinary skill in the art can screen different combinations of amino acid substitutions in position 226-229 which is the epitope recognition site using methods known in the art for introducing random or arbitrary substitutions into SEB to reduce reactivity to IgG antibody and the motivation to mutate position 23 as taught by Sasaki et al is that amino acid substitution at position 23 results in a SEB that has inhibitory activity on T cell activation with reduced toxicity.

The closest prior art that discloses the amino acid sequence of unmodified SEB is by Terman et al and the difference between the prior art wild type sequence (see Appendix A) and that of instant SEQ ID NO: 1 is a single amino acid mismatch at position 123). SEQ ID NO: 1 would have been prima facie obvious to obtain and is prima facie obvious over the SEB amino acid sequence disclosed by Terman et al. There would have been only a limited number of species of the SEB protein and the generic teaching to modify a SEB protein for various advantageous reasons would make the species of SEB protein i.e. SEQ ID NO: 1 prima facie obvious.

The resulting modified SEB would have the same structure as claimed and possess reduced reactivity with a neutralizing anti-SEB antibody and capable of being expressed in a soluble form in *E. coli* so as to be maintained stably in aqueous solution and retains a therapeutic effect to rheumatoid arthritis.

Status of Claims

Claims 6-8, 16-17 and 21 are rejected. Claim 23 is withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to OLUWATOSIN OGUNBIYI whose telephone number is (571)272-9939. The examiner can normally be reached on M-F 8:30 am- 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Oluwatosin Ogunbiyi/
Primary Examiner, Art Unit 1645